

REMARKS

Claims 1 – 5, 8, 9, 11 – 32, 44 – 62, and 64 – 71 are pending. Claims 1, 11, 12, 31, 32, 44, 59, 64, and 65 are currently amended and claims 10 and 63 have been cancelled by this amendment. Support for the amendments is found throughout the specification as originally filed. Applicants respectfully submit that no new matter is presented thereby. Entry of the amendments is respectfully requested.

As a preliminary matter, Applicants would like to draw the Examiner's attention to the Information Disclosure citations submitted 5/21/02 and 11/25/02. It is respectfully requested that the status of these two IDS citations be indicated by the Examiner in the next Office Action

Claims 1-3, 6-15, 17,18, 20-22, 27-30, 32, and 44-52 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7-23, 25, 27, 28-30, 34-37, and 41-45 of copending application Serial No. 09/568,818. Applicants respectfully submit a timely response will be filed upon allowance of claims if necessary.

Applicants would like to thank the Examiner for the courtesies extended in the interview of April 25th. As discussed in the interview, the present invention is directed, at least in part, to the unexpected findings as to the enhanced physical stability and dispersibility of phospholipid formulations containing a metal ion-lipid complex. Such physical stability is extremely important in the case of pharmaceutical products, which must remain storage stable throughout their shelf-life. Physical stability is also of particular importance to particulates intended for pulmonary administration as such particulates must be highly dispersible and maintain satisfactory aerosol performance, as measured by their geometric and aerodynamic diameters, for example. The enhanced stability achieved by the present invention is nowhere disclosed or suggested in the prior art as discussed in detail below.

Claims 1-5,8,9,15,19-25, 27 and 31 have been rejected under 35 U.S.C. §102 (b) as being anticipated by Elstetter (AU 714998). The compositions disclosed in Elstetter are a mixture of saturated and unsaturated phospholipids. Such mixtures do not disclose or suggest a storage stable composition comprising a saturated, zwitterionic phospholipid and a polyvalent cation at a molar ratio of polyvalent cation to phospholipid of at least 0.05 as currently claimed. Applicants respectfully submit that this rejection should be withdrawn.

Claims 1-5, 8 – 32 and 44-71 have been rejected under 35 U.S.C. §103 (a) over Weers et al. The Examiner states that Weers et al. teach that adding salts fine tunes the stabilized dispersions disclosed therein for maximum life and ease of administration, thereby rendering the present invention obvious. This rejection is respectfully traversed for the reasons that follow.

Applicants have amended the claims to recite that the compositions comprise a molar ratio of polyvalent cation to phospholipid of at least 0.05. Weers et al. is silent as to any teaching of molar ratios as claimed. Furthermore, the unexpected results attributed to the addition of calcium chloride in such amounts are nowhere disclosed or suggested in Weers et al.

It is quite unexpected that the addition of a very hygroscopic salt such as calcium chloride to a dry powder prone to moisture induced destabilization would provide beneficial stabilization properties to the dry powder. This is described at page 8, lines 7-28 of the specification as filed. As seen at page 9, lines 18-22, the present inventors have observed that the gel to liquid crystal transition temperature of the phospholipid can be manipulated by varying the amount of metal ion in the formulation in order to obtain phospholipid-based dry powders that both flow well and are readily dispersible.

In addition to the significant increase in T_m of saturated phospholipids due to the addition of metal ions, the present inventors have found that the addition of metal ions to

saturated phospholipids maintains these elevated order-to-disorder transition temperatures of the phospholipids constant as a function of water content. The superior physical stability and protection from water provided by the addition of metal ions to saturated phospholipids further illustrates the unexpected results of the present invention.

Applicants had previously submitted a §1.132 declaration (the “Weers declaration”) directed to the unexpected results attributed to the present invention in support of the previous response. As discussed in detail in the Weers declaration, the beneficial results regarding physical stability resulting from the use of metal ions such as calcium with saturated phospholipids were both superior to and unexpected from the use of such metal ions with unsaturated phospholipids. Applicants believe the Weers declaration remains probative evidence of the non-obviousness of the invention as currently claimed.

In particular, paragraph 9 of the Weers declaration included the following statement:

“Based upon these results and for the reasons set forth above, it is my opinion that the unexpected benefits attributed to the addition of calcium chloride to saturated phospholipids would not have been obvious to one of ordinary skill in the art at the time of the invention.”

The Examiner is currently relying upon Weers et al. (U.S. Patent No. 6,309,623), in making the current obviousness rejection. Weers et al. was relied upon by the Examiner in the prior Office Action to which the declaration was addressed. The previously submitted Weers declaration remains probative on the issue of non-obviousness of the instant invention.

This is seen at paragraph 5 of the Weers declaration where Weers et al. is specifically referenced. Thus, it is respectfully submitted that the previously submitted Weers declaration remains probative evidence of secondary considerations of non-obviousness. Thus, for all of the reasons set forth above and in the previously submitted

Weers declaration, Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

Claims 1-3, 8,9, 15-17 and 31 have been rejected 35 U.S.C. §103 (a) as being obvious over Gould-Fogerite et al. Gould-Fogerite et al. discloses cochleates comprising anionic phospholipids. A preferred embodiment of the present invention is directed to saturated phospholipids, as disclosed for example at page 9, lines 1-17. Applicants have further amended the claims to recite that the saturated phospholipids are zwitterionic and that the compositions comprise phospholipid and a polyvalent cation at a molar ratio of polyvalent cation to phospholipid of at least 0.05. Applicants respectfully submit that this rejection has been overcome and should be withdrawn.

Applicants believe that all of the pending claims are presently in condition for allowance. If it is believed that this will expedite prosecution of the present application, the Examiner is invited to telephone the undersigned attorney at the number below.

Respectfully submitted,

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